

Clinical follow up of Mexican women with early onset of breast cancer and mutations in the BRCA1 and BRCA2 genes

Ana Laura Calderón-Garcidueñas, MD, MSc,^(1,2) Pablo Ruiz-Flores, MD, PhD,⁽³⁾ Ricardo M Cerda-Flores, PhD,⁽²⁾ Hugo A Barrera-Saldaña, PhD.⁽⁴⁾

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Abstract

Objective. This study describes the presence of mutations in BRCA1 and BRCA2 genes in a group of Mexican women and the clinical evolution of early onset breast cancer (EOBC). **Material and Methods.** A prospective hospital-based study was performed in a sample of 22 women with EOBC (7 in clinical stage IIA, 8 in IIB, and 7 in IIIA). The patients attended a tertiary care hospital in northeastern Mexico in 1997 and were followed up over a 5-year period. Molecular analysis included: 1) a mutation screening by heteroduplex analysis (HA) of BRCA1 and BRCA2 genes and 2) a sequence analysis. **Results.** Of 22 patients, 14 (63.6%) showed a variant band detected by heteroduplex analysis of the BRCA1 and BRCA2 genes: 8 polymorphisms, 4 mutations of uncertain significance, and 2 novel truncated protein mutations, one in BRCA1 (exon 11, 3587delT) and the other in the BRCA2 gene (exon 11, 2664InsA). **Conclusions.** These findings support future studies to determine the significance and impact of the genetic factor in this Mexican women population.

Key words: breast cancer; BRCA genes; Mexico

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Resumen

Objetivo. Describir la presencia de mutaciones en los genes BRCA1 y BRCA2 y la evolución clínica de un grupo de mujeres con carcinoma mamario de inicio temprano (CMIT). **Material y métodos.** Se realizó un estudio hospitalario, prospectivo, en una muestra de 22 pacientes con CMIT (siete en etapa clínica IIA, ocho en la IIB y siete en etapa IIIA). Las pacientes fueron atendidas en un hospital del noreste de México en 1997 y se realizó un seguimiento clínico durante cinco años. El análisis molecular incluyó: 1) análisis heterodúplex (AH) para detectar bandas variantes en la secuencia de ADN de los genes BRCA1 y BRCA2, y 2) análisis de secuenciación. **Resultados.** De 22 pacientes, 14 (63.6%) mostraron banda variante por AH en los genes BRCA1 y BRCA2: ocho polimorfismos, cuatro mutaciones de significado incierto y dos mutaciones novedales con proteína truncada, una en BRCA1 (exón 11, 3587delT) y otra en BRCA2 (exón 11, 2664InsA). **Conclusiones.** Estos hallazgos apoyan el desarrollo de futuros estudios para determinar el impacto del factor genético en la población mexicana con CMIT.

Palabras clave: cáncer de mama; genes, BRCA; México

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(1) Department of Pathology, Hospital de Especialidades No. 25, Instituto Mexicano del Seguro Social (IMSS), Monterrey, Nuevo León, México.

(2) Department of Population Genetics, Northeastern Center for Biomedical Research, IMSS, Monterrey, Nuevo León, México.

(3) Center for Biomedical Research, Department of Genetics, Medical School, Autonomous University of Coahuila, Torreón, Coahuila.

(4) Department of Biochemistry, Medical School, Universidad Autónoma de Nuevo León. Monterrey, Nuevo León, México.

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Address reprint requests to: Prof. Dr. Hugo A Barrera-Saldaña. Departamento de Bioquímica. Facultad de Medicina de la Universidad Autónoma de Nuevo León. Avenida Madero y Dr. Eduardo Aguirre Pequeño, colonia Mitras Centro 64460, Monterrey, Nuevo León, México.

E-mail: hbarrera@fm.uanl.mx

Breast cancer (BC) has evolved as one of the main causes of morbidity and mortality for women. Each year, at least a million women are diagnosed with this disease in the world and the number of deaths is estimated in 300 000.¹ Annually, 180 000 new cases and 30 000 deaths are reported in the United States.²

Mexico is a country with almost 98 million inhabitants; 51.1% are women.³ In 1993, the number of new BC cases registered was 5 739 and 20% of them were residing in the state of Nuevo León.⁴ In 1998, yearly cases increased to 9 490.⁴ The average BC mortality rate in Mexico is 10.45 /100 000 women. Nuevo Leon ranks third in mortality rate due to this cancer in the country, with 15.9/100 000 inhabitants, following by Mexico City and the state of Coahuila. The mortality rates due to BC are higher in the Northern states: Coahuila (16.1), Nuevo Leon, Sonora (14.5), Chihuahua (14.1), and Baja California (13.5).⁴

Increasing age is a major risk factor for BC. The risk of developing the disease is 1 in 20 000 for women younger than 25 years and this risk increases to 1 in 9 women older than 79 years.⁵ However, in 1998 in Mexico,⁴ 8% of all breast cancer cases presented in the early onset (EOBC) group (35 years of age or earlier at diagnosis). Many studies have demonstrated that BC in young patients has a more aggressive clinical course than in older patients.⁵ It is thought that tumors in younger women are biologically different, frequently with a higher proliferation index and less histological differentiation. In general, EOBC patients have shorter disease-free and reduced survival times.⁵

On the other hand, heredity is another important risk factor for BC. It is estimated that it contributes 3 to 10% to BC cases and up to 30% to early onset ones.⁶ Mutations in BRCA1 and BRCA2 genes are responsible for 90% of the inherited BC cases.⁷

Since there is a lack of information in Mexico about the contribution of BRCA1 and BRCA2 genes to BC, the aim of this case series, prospective, hospital-based study of 22 Mexican women with EOBC was to describe the clinical course of BC and the presence of mutations of the BRCA1 and BRCA2 genes.

Material and Methods

Our protocol was reviewed and approved by the Scientific and Ethics Committee of the Hospital of Specialties # 25, Mexican Institute of Social Security (IMSS). In our hospital an average of 250 new breast cancer cases are studied per year and 25 of them are women with EOBC. A sample of 22 consecutive women newly diagnosed with histologically confirmed EOBC, aged 35 years or younger at the time of diagno-

sis, was recruited from the hospital in 1997. The study design and objectives were explained to the patients who were asked to sign an informed consent. The clinical histories were obtained and followed up for 5 years. Also, each patient donated 15 ml of venous blood from which DNA was extracted.⁸ Mutations in the BRCA1 and BRCA2 genes were screened for by the heteroduplex analysis (HA). Variant bands observed in the HA were re-amplified and sequenced.⁹

Clinical and pathological data. Patients were interviewed by two of the authors (ALCG, PRF); a questionnaire was completed and patients' medical records were examined. Age at diagnosis and data about the clinical progress and outcome were also recorded. The tumor size was measured in centimeters at its largest diameter. All breast tumor slides were reviewed by one of the authors (ALCG). Tumors were classified histologically and recorded as ductal or lobular and subtypes of ductal carcinomas.¹⁰ The histological grade of differentiation of tumors was determined according to the modified Bloom-Richardson criteria.¹¹ In the mastectomy specimen, the total numbers of lymph nodes, as well as the number of specimens with metastasis were recorded. The sites of metastasis were also described. Patients attended the hospital at least four times during the first year following diagnosis, and twice each subsequent year.

Results

Clinical characteristics. Table I shows the more important clinical and tumoral findings. The identification number (ID) of patients is given in Tables II and III. All patients accepted to participate in the study and none were lost during 1997-2002. The age range was 24 to 35 years; 68% of patients completed elementary school and 82% were housewives. History of BC in the family was present in six out of 22 cases (27%) and two out of 22 (9%) patients had a first degree relative with BC. Of the two women with truncated protein mutations (TPM), the one involving the BRCA1 gene had only a paternal aunt with BC, while the other, who had the mutation in the BRCA2 gene, had a history of gastric and breast carcinoma in two paternal aunts; in the maternal line, she had two aunts with breast cancer, and one uncle with melanoma. Diabetes mellitus and arterial hypertension affected 9% of patients. Twenty patients had children (range 1-5) and the other two had not initiated active sexual life. Forty percent of patients with children breast-fed them. Eighty-six percent of patients did not smoke. According with the Bray classification, 36% of the patients had normal weight, 27% obesity grade I, 28% grade II, and 9% grade III.

Table I
**CHARACTERISTICS OF PATIENTS WITH EARLY ONSET
 BREAST CANCER (1997- 2002).
 HOSPITAL OF SPECIALTIES #25,
 MEXICAN INSTITUTE OF SOCIAL SECURITY**

Characteristics	No.	%
Age at diagnosis (years, median)	32 ± 3	(24- 35)
Survival		
Yes	12	(54.55)
No	10	(45.45)
Clinical stage		
IIA	7	(31.82)
IIB	8	(36.36)
IIIA	7	(31.82)
Tumor size (cm, median) 5.20 ± 1.56 (2.5-8)		
Histological type		
Lobular	1	(04.55)
Ductal NOS*	16	(72.73)
Ductal comedo type	3	(13.64)
Ductal medullar type	2	(09.09)
Grade of tumor differentiation†		
Moderate	11	(52.38)
Poor	10	(47.61)
Lymph node metastasis		
Yes	11	(50)
No	11	(50)
Systemic metastasis sites		
0=	9	(40.91%)
1=	5	(22.73%)
Various=	8	(36.36%)

* No otherwise specified

† Grade of tumor differentiation according to the modified Richardson-Bloom classification for ductal carcinomas¹¹

Tumor histology. Twenty-one tumors were classified as ductal carcinomas and the remaining one as lobular in origin (Table I). Ductal carcinomas were poorly and moderately differentiated in 10 out of 22 and 11 out of 22 cases, respectively. The two women with TPMs had a classical invasive lobular carcinoma (BRCA1 gene mutation) and a medullar carcinoma (BRCA2 gene mutation). The medullar carcinoma showed non-caseous granulomas distributed within the tumor and around

Table II
**DESCRIPTIONS OF THE BRCA1 AND BRCA2
 GENE MUTATIONS. HOSPITAL OF SPECIALTIES #25,
 MEXICAN INSTITUTE OF SOCIAL SECURITY, 1997-2000**

ID	BRCA gene	Gene site*	Mutation Type†	Mutation Nature§	Protein Effect#
1	2	27	MS/P	A10462T	Ile3412Val
2	2	27	MS/P	A10462T	Ile3412Val
3	2	27	MS/P	A10462T	Ile3412Val
4	2	22	MS/P	G9079A	Ala2951Thr
5	2	10	MS/P	A1093C	Asn289His
	2	11	MS/P	A3199G	Asn991Asp
	2	22	MS/P	G9079A	Ala2951Thr
6	2	27	P-silent	C9966T	Ala3246Ala
7	1	IVS7	Intr-P	CIVS7-34T	Unknown
	2	10	Ms/P	A1093C	Asn289His
	2	11	MS/P	A3199G	Asn991Asp
8	1	IVS7	Intr-P	CIVS7-34T	Unknown
	2	Intr 18	Intr-P	C8715+47T	Unknown
	2	27	NS/P	A10204T	Lys3326X
9	2	19	MS/USM	G8605A	Gly2793Arg
10	2	12	MS/USM	T7105C	Phe2293Leu
11	2	27	MS/USM	C10349T	Thr3374Ile
12	1	11	MS/USM	G2364T	Asp749Tyr
	2	27	MS/P	A10462T	Ile3412Val
13	2	11	FS	2664InsA	ter826
14	1	11	FS	3587delT	ter1159

* Locus or intronic region

† MS: missense mutation, NS: nonsense mutation, FS: frame shift mutation, USM: uncertain significance mutation, P: polymorphism, intr: intron

§ A: adenine, T: thymine, C: cytosine, G: guanine, del: deletion, Ins: insertion

ter: premature stop codon, Ile: isoleucine, Val: valine, Asn: asparagine, His: histidine, Asp: aspartate, Ala: alanine, Lys: lysine, Thr: threonine, Phe: phenylalanine, Leu: leucine, Gly: glycine, Arg: arginine

its border. Special stains for fungi, tuberculosis bacilli, and bacteria were negative.

DNA data. Table II shows a description of the mutations found for the BRCA1 and BRCA2 genes. Only 14 of the 22 patients showed a variant band when the mutations in the BRCA1 and BRCA2 genes were screened by the heteroduplex analysis. Thus, 64% of patients with EOBC had variations in the DNA sequence involving BRCA1 or BRCA2 genes. The molecular findings were: 8 patients had one or more polymorphisms, 4 women had mutations of uncertain significance (USM) and 2 other had 2 novel TPM, one in BRCA1 (exon 11, 3587delT) and the other in BRCA2 gene (exon11, 2664InsA). In general, exclusively BRCA2 variant bands were found in 71.4% of the cases, versus only 7.14% of BRCA1 vari-

ants; in 21.43%, patients had both BRCA1 and BRCA2 variant bands. Polymorphisms were more frequently found in the BRCA2 gene, especially in exon 27, followed by exons 11, 10 and 22. The TPM affected exon 11 in BRCA1 and BRCA2 genes.

Table III shows the clinical stage and molecular findings in BRCA1 and BRCA2 genes and Table IV summarizes the molecular findings according with the clinical stage.

Table III
CLINICAL EVOLUTION AND MOLECULAR GENETIC FINDINGS. HOSPITAL OF SPECIALTIES #25, MEXICAN INSTITUTE OF SOCIAL SECURITY, 1997-2000

ID	Age*	Alive	CS†	DNA findings‡	T#/DG&	Metastasis: site
1	30	Yes	IIA	BRCA2 polymorphism	D/M	None
2	34	Yes	IIA	BRCA2 polymorphism	D/M	None
3	24	Yes	IIA	BRCA2 polymorphism	D/M	Lungs
12	34	Yes	IIA	BRCA1 USM	D/M	None
18	34	Yes	IIA	normal	D/M	None
19	24	No	IIA	normal	D/M	Lung, liver, bones, lymph nodes
22	31	Yes	IIA	normal	D/P	None
4	35	Yes	IIB	BRCA2 polymorphism	D/M	None
9	30	Yes	IIB	BRCA2 USM	D/P	Ribs, lungs
10	33	No	IIB	BRCA2 USM	D/M	Lumbar vertebral bones
11	33	No	IIB	BRCA2 USM	D/P	Lungs
13	32	Yes	IIB	BRCA2 TPM	Med	None
14	29	Yes	IIB	BRCA1 TPM	Lob	None
16	34	Yes	IIB	normal	D/P	Liver
17	35	No	IIB	normal	D/P	Cerebellum, pleura, pericardium
5	33	No	IIIA	BRCA2 polymorphism	D/P	Liver
6	33	No	IIIA	BRCA2 polymorphism	D/M	Bones, skin
7	34	Yes	IIIA	BRCA2 polymorphism BRCA1 polymorphism	D/M	None
8	34	No	IIIA	BRCA2 polymorphism BRCA1 polymorphism	D/P	Skull, liver
15	29	No	IIIA	normal	D/M	Brain, kidneys, liver
20	27	No	IIIA	normal	D/M	Bones
21	35	No	IIIA	normal	D/P	Brain, lungs, bones

* age at diagnosis in years

† clinical stage at diagnosis

‡ USM= uncertain significance mutation, TPM= truncated protein mutation

T= Type of tumor= Ductal (D) no otherwise specified, Med= medullar carcinoma, Lob= lobular

& grade of tumor differentiation according to Richardson-Bloom classification, M= moderately differentiated, P= poorly differentiated

Table IV
CLINICAL STAGE AND NUMBER AND TYPE OF MOLECULAR FINDINGS IN BRCA1 AND BRCA2 GENES. HOSPITAL OF SPECIALTIES #25, MEXICAN INSTITUTE OF SOCIAL SECURITY, 1997-2000

Clinical stage	Dead women/total	Significant mutation	USM ^a	Polymorphisms
IIA	1/7	0	1	3
IIB	3/8	2 ^b	3	1
IIIA	6/7	0	0	4

^a Uncertain significance mutation

^b Frame shift type

All patients in the same clinical stage received the same treatment, including modified radical mastectomy, chemotherapy (5-fluoracil, epirubicin, cyclophosphamide) and radiotherapy. The five-year mortality among these women was about 45%. Table IV shows the number of dead women/total with the clinical stage at diagnosis (1/7 in IIA, 3/8 in IIB and 6/7 in IIIA). All deaths were caused by neoplastic activity and 80% occurred within the first 3 years following diagnosis. Fourteen patients developed metastatic disease, and among those, only 4 still remain alive.

Discussion

This follow-up study characterized 22 young women with EOBC who attended a tertiary care hospital in northeastern Mexico. Even though the results of this study cannot be extrapolated to the population at large, it provides useful information on which to base further studies.

Several risk factors particular to this group were observed. Obesity is a BC risk factor in postmenopausal women but apparently not in young women;¹² nevertheless, 14 out of 22 of our women had some degree of obesity. The prevalence of family history of BC in our patients was similar to those previously reported among Mexican women¹³ and similar to American and European studies.¹⁴ The prevalence of common diseases such as diabetes mellitus and arterial hypertension was similar to that reported in adults in the north of Mexico.¹⁵

With one exception, all fatalities had lymph node metastases (LNM) at diagnosis. The sole exception initially underwent partial lymph node resection, with only six non-metastatic lymph nodes dissected after careful examination of axillary fat; later, developing

ipsilateral LNM and systemic dissemination. On the other hand, two patients initially presenting with LNM survived, one of whom remained asymptomatic at the end of the study, and the other, who had a poorly differentiated neoplasm, developed liver metastasis and had terminal disease. These outcomes are consistent with those reported in the relevant literature. In general, metastatic involvement of axillary lymph nodes is one of the most important prognostic factors for survival in BC. Without LNM, 5-year survival is about 80%, with one to three positive lymph nodes is 50% and only 21% with four or more nodes.¹⁶

In general, the frequency of mutations in BRCA1 and BRCA2 genes in our study sample seems to be very similar to that described in other studies of EOBC,¹⁷⁻¹⁹ however, some of these mutations had not been described before (the two PTM and gly2793Arg in BRCA2 gene and Asp749Tyr in BRCA1 gene) and this can be explained by the genetic characteristic of our mestizo population.²⁰ If we consider only those mutations resulting in truncated proteins, BC in our patients was associated with mutations of BRCA1 and BRCA2 genes in 9 % of cases, which is also consistent with the percentage of cases in the literature attributable to these types of mutations in these genes.^{17,18} Overall, depending on the population analyzed, the estimated percentage of mutations in young women with breast cancer is between 6 and 30%.¹⁹

As was mentioned before, the two truncating protein mutations detected in our Mexican women have not been reported previously in other countries.²¹ Since these women originated from northeastern Mexico, and had resided there for at least four generations, our observations may be identifying unique population mutations. In relation with the four cases with USM, further studies are needed to determine whether they correspond to clinically significant mutations or polymorphisms.

All the reported polymorphisms were in the BRCA2 gene, although some women also had them in the BRCA1 gene. It is well known that in different populations, the contribution of BRCA1 and BRCA2 genes may be different not only in polymorphisms but also in deleterious mutations; thus, in Jewish women, BRCA1 mutations are more frequent than BRCA2 ones, while in Italian women, the contribution of BRCA2 mutations predominates.²² The study of polymorphisms is important especially in a mestizo population, such as the Mexican case. Some of the polymorphisms described in these patients (CIVS7-34T in BRCA1 and A1093C in BRCA2 genes) have been previously described in Spain and elsewhere,²¹ including Africans (C8715+47T),²¹ thus denoting the influence of these origins.²⁰

Early studies of women with mutations in BC susceptibility genes did not show differences between sporadic and mutation-associated tumors.²³ More recent quantitative studies reveal higher nuclear grade, less positive expression to estrogen receptors, more pleomorphism and higher mitotic index in tumors associated with mutations than in sporadic tumors.²⁴ One of our two cases had a lobular carcinoma (BRCA1 mutation) and the other a medullar carcinoma (BRCA2 mutation). Both of these histological tumor types have a better prognosis than the common ductal adenocarcinoma. Furthermore, the observation of non-caseous granulomas in the tumor probably signals active anti-tumor cellular immunity, and more importantly, these patients were among the survivors and are now clinically asymptomatic.

Conclusions

In summary, our study shows that breast cancer behaves aggressively in young Mexican women, particularly if the disease is clinically advanced at the time of diagnosis.¹⁶ We have also demonstrated the contribution of BRCA1 and BRCA2 genes in EOBC in Mexican patients. Although there are reports of mutations in Mexican-American women,²⁵ this study is the first to describe both, the clinical progress and the molecular genetic analysis of BRCA1 and BRCA2 genes in Latin-American women. The two novel mutations were associated with less aggressive types of adenocarcinoma and non-metastatic, localized disease, in spite of a large tumor size. The ability to identify women with mutations allows further study of the family and, thus, early intervention, hopefully leading to a reduction in mortality.²⁶

Our data point to the need for a large population-based study to characterize the EOBC in Mexican women, in order to determine the type, frequency, and significance of variations in the sequences of BRCA1 and BRCA2 genes in Mexico.

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